

Selection against Deleterious Mutations and the Maintenance of Biparental Sex

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The mutational deterministic hypothesis postulates an advantage to sexual over asexual reproduction when mutation rates are on the order of 1.0 per genome per generation, provided that selection takes the form of a synergistic epistasis. While the efficacy of this mechanism has been investigated for infinite populations, its ability to protect sex in finite populations exhibiting stochastic dynamics remains untested. Stochastic processes have the potential to undermine protection for sex in two ways: (1) asexual lineages derived from sexual ancestors may, by chance, be founded by individuals bearing fewer than the equilibrium mean number of mutations, and (2) once established, such lineages will undergo random perturbations in the rates at which they grow and accumulate mutations. In the present study, I show using computer simulation that sexual populations of as many as 10,000 individuals are susceptible to invasion by asexual lineages for mutation rates higher than predicted under the mutational deterministic hypothesis. My simulations differ from previous investigations in that they model the progress of asexual lineages into sexual populations as both stochastic and deterministic processes for various mutation rates, selection regimes, and population sizes. It is suggested that ecological factors, such as parasitism or release from competition, could interact with selection against deleterious mutations to protect sex. To provide the sole explanation for sex, however, may require that selection against deleterious mutations be accompanied by mutation rates on the order of 2.0 per genome per generation. © 1994

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INTRODUCTION

Sexual reproduction is less efficient than asexual reproduction because of the cost associated with the production of males (Maynard Smith, 1978) or the reduction in parent–offspring relatedness due to meiosis and syngamy (Williams, 1975), depending on the type of asexual offspring (Lively and Lloyd, 1990). This handicap, known as the “cost of sex,” may be as great as two-fold when males contribute nothing to raising offspring. Why then, given the potential for organisms to propagate themselves more

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efficiently through parthenogenesis, does sexual reproduction enjoy such a widespread distribution across so many taxa (see Bell, 1982; Maynard Smith, 1978)? Attempts to answer this question have led evolutionary biologists to search for an adaptive explanation to sex, presumably brought about through segregation and recombination between chromosomes of cross-fertilizing organisms. One possibility is that sex is adaptive because it leads to the increased efficiency of selection against deleterious mutations (e.g., Muller, 1964; Kondrashov, 1982, 1988, 1993). In recent years one mutational model, the mutational deterministic hypothesis (Kondrashov 1982, 1988), has gained support as a general explanation for the maintenance of sexual reproduction.

The mutational deterministic hypothesis postulates an advantage to sexual reproduction sufficient to offset the two-fold cost when deleterious mutation rates (U) are on the order of 1.0 per genome per generation, provided that each additional mutation results in a larger decrease in relative fitness (i.e., synergistic epistasis) (Kondrashov, 1982). The advantage is greatest under truncation selection, where individuals with more than k mutations die, and the rest are equally viable; the advantage decreases as synergistic interactions among mutations become less extreme (Kondrashov, 1982). Synergistic epistasis can lead to a decreased mutation load (L) if the equilibrium variance for genome contamination (number of deleterious mutations per individual) is high, because fewer individuals must be culled by selection to counterbalance a given mutation rate (Crow and Kimura, 1979). In the absence of sexual reproduction, however, synergistic epistasis erodes the equilibrium variance for genome contamination, and the mutation load is not reduced (Kondrashov 1988, 1993). More generally, Kimura and Maruyama, 1966, showed that the equilibrium mutation load for an asexual population is exactly $1 - e^{-U}$, regardless of the type of selection. Sexual reproduction, on the other hand, maintains a larger equilibrium variance for genome contamination, and the mutation load in a sexual population (L_{sex}) can be much smaller than for an asexual population (L_{asex}) for mutation rates on of order 1.0 per genome per generation or greater (Kondrashov, 1982, 1993). The disparity between L_{sex} and L_{asex} increases as U grows larger, and is sufficient to offset the two-fold cost of sex when $(1 - L_{\text{sex}})/(1 - L_{\text{asex}}) > 2$ (Kondrashov, 1982, 1988).

Kondrashov (1982) calculated the advantage to sexual reproduction by comparing the equilibrium mutation loads of infinite sexual and asexual populations. However, the assumption that asexual populations are initially at equilibrium under mutation-selection balance is likely to be violated in nature, because asexual lineages are typically derived from sexual ancestors (Bell, 1982; Johnson, 1992; Maynard Smith, 1978; Williams, 1975) and the number of mutations in founders will be drawn from the distribution of genome contamination in the parent sexual

population. Because equilibrium sexual populations have a lower mean and higher variance for genome contamination than asexual populations (Kondrashov 1982, 1988), this number may deviate widely from the equilibrium mean value for asexual populations. Asexual founders which, by chance, harbor few mutations may give rise to lineages that are able to invade and displace parent sexual populations before the mutation load grows large enough to undermine the two-fold advantage of parthenogenesis.

Kondrashov (1982) and Charlesworth (1990) recognized this problem and employed deterministic numerical simulations to examine conditions under which sexual populations were protected against invasion by asexual lineages started with fewer than the equilibrium mean number of mutations. Kondrashov's (1982) simulations led him to conclude that for linear selection with $U=2.0$ and $k=20$ (individuals with k or more mutations are inviable), sexual populations are protected from invasion by asexual populations started with 10 mutations. Charlesworth's (1990) simulations tracked the progress of asexual lineages started at frequencies of $1/N$, where $N=10^3$, 10^4 , and 10^5 , into equilibrium sexual populations. His standard parameters included a mutation rate of $U=1.5$ under an exponential-quadratic fitness function similar to that studied by Kimura and Maruyama (1966). In Charlesworth's (1990) simulations, sexual populations of sizes $>10^3$ were protected against invasion by asexual lineages started with fewer than the mean equilibrium number of mutations.

In the present study, I also relax the assumption that asexual populations are initially at equilibrium under mutation–selection balance. In addition, I model the progress of asexual lineages into sexual populations as both a stochastic and deterministic process for various combinations of mutation rates, selection regimes, and population sizes. My stochastic simulations differ from the deterministic models of Kondrashov (1982) and Charlesworth (1990) in that they allow for random perturbations in the rates at which populations grow and accumulate mutations. Results from this study suggest that stochastic processes have the potential to undermine protection for sex in populations comprised of as many as 10,000 individuals. To provide the sole explanation for sex, selection against harmful mutations may require mutation rates on the order of 2.0 per genome per generation.

THE MODELS

I used computer simulation to examine conditions under which asexual lineages started with fewer than the equilibrium mean number of mutations can invade and displace sexual populations from which they are derived.

The importance of stochastic processes was evaluated by comparing stochastic and deterministic runs of the simulation for various combination of mutation rates, selection regimes, and population sizes.

Stochastic Model

In the stochastic simulations, the computer kept track of a population of N haploid individuals that were either sexual hermaphrodites or asexual females. Generations were modeled as discrete and individuals exhibited life cycles that followed a pattern of mutation–reproduction–selection. The genomes of individuals contained 500 loci at which mutations could potentially accumulate. With the exception of the two-fold cost of sex, relative fitnesses of individuals within populations differed only with respect to the number of mutations present in the genome.

Three types of selection regime were examined in this study: truncation, intermediate, and exponential-quadratic (Fig. 1). Truncation selection, the most extreme form of synergistic epistasis, is important because it generates the greatest advantage to sex (Kondrashov, 1982, 1988). Intermediate (Kondrashov, 1982) and exponential-quadratic selection (Charlesworth, 1990) are considered because they represent less extreme forms of synergistic epistasis. Although there are virtually no data supporting the existence of truncation selection in nature, data from experiments on *Drosophila melanogaster* (Mukai, 1969) and RNA viruses (Chao, 1988) suggest that mutations may interact synergistically.

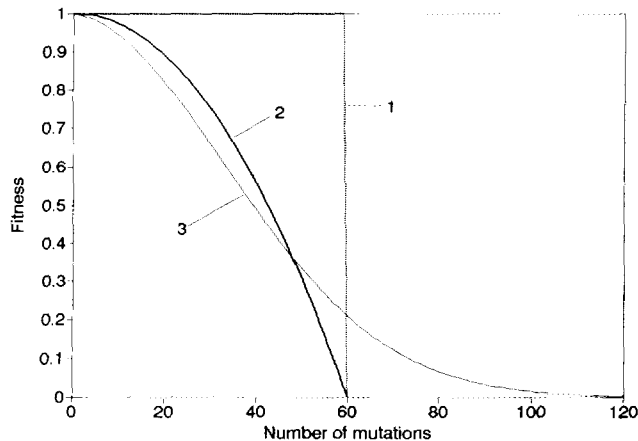


FIG. 1. Fitnesses of individuals with different numbers of mutations (n) under truncation ($w(n) = 1 - (n/k)^\alpha$, $\alpha = 1000$) (1) intermediate ($w(n) = 1 - (n/k)^\alpha$, $\alpha = 2$) (2) and exponential-quadratic ($w(n) = \exp - (\alpha n + \frac{1}{2} \beta n^2)$, $\alpha = 0.002$, $\beta = 0.0008$) (3) selection. For truncation and intermediate selection, individuals with more than k mutations are inviable.

Sexual individuals underwent a life cycle of syngamy and meiosis during which free recombination occurred in diploid zygotes. Following recombination, zygotes underwent a reduction division to give rise to a single haploid juvenile. Asexual life cycles lacked meiosis and syngamy, and offspring were derived in a manner equivalent to mitotic divisions of unfertilized haploid ova. Sexual individuals produced an average of 10 outcrossed eggs and achieved 10 cross-fertilizations through male function during their lifetimes, while asexuals produced an average of 20 apomictic eggs. The two-fold cost of sex arose from the allocation of 50% of resources to male function in hermaphrodites.

During each generation, the chance for any adult to reproduce followed a Poisson distribution with a mean of 1.0. Once an individual (asexual reproduction) or pair of individuals (sexual reproduction) had been selected for reproduction, mutations were allowed to occur randomly in the genome with probability U , where U is the Poisson-distributed mutation rate per genome per generation. Offspring were subjected to selection against mutation and survivors pooled into an array. At the end of a generation, offspring were chosen randomly from the array to settle into each of N available sites to become the next generation of adults; supernumerary individuals died.

At the beginning of each run, a population of $N - 1$ (where $N = 10^3$ or 10^4) sexuals was initialized to an equilibrium state with respect to genome contamination. At the end of the first generation, a single asexual founder was introduced into the sexual population. Founders were initialized with a number of mutations approximately equal to two standard deviations less than the mean for the equilibrium sexual population with which they were competed, as the transition to asexuality is unlikely to occur in an ancestor bearing fewer mutations (Charlesworth, 1990). At the end of each generation, the numbers and types of individuals in the population and their population means for genome contamination were written to a computer file. Runs were conducted for mutation rates of $U = 1.0, 1.5,$ and 2.0 for threshold, intermediate, and exponential quadratic selection. Population sizes of 10^3 and 10^4 were investigated for each combination of parameters.

Deterministic Model

The deterministic simulations used in the present study were similar to those employed by Kondrashov (1982) and Charlesworth (1990). Asexual lineages bearing a number of mutations equivalent to approximately two standard deviations less than the equilibrium mean value for sexual populations with which they were competed were initialized at frequencies of $1/N$, where $N = 10^3$ or 10^4 . As in the stochastic model, in the absence of selection against mutation, asexuals enjoyed a two-fold reproductive

advantage over sexuals. The trajectories of asexual lineages into the sexual populations were determined by iterating the equations of Kimura and Maruyama, 1966, in which the frequency of asexual individuals having i mutant genes in the next generation is computed as

$$f_i' = \sum_{j=0}^i \frac{w_{i-j} f_{i-j}}{\bar{w}} \frac{U^j}{j!} e^{-U},$$

where the mean fitness of the population is

$$\bar{w} = \sum_{j=0}^{\infty} f_j w_j.$$

Following Charlesworth's (1990) methodology, fixation of an asexual lineage was assumed to occur if the frequency of sexuals fell below the initial frequency ($1/N$) of asexuals in the population.

RESULTS

Results from stochastic and deterministic runs of the computer simulations for 14 different combinations of mutation rates, selection regimes, and population sizes are summarized in Table I. Each combination of parameters is sufficient to generate an advantage to sexual reproduction under Kondrashov's (1982) treatment of infinite equilibrium sexual and asexual populations. Starting asexual lineages with fewer than the equilibrium mean number of mutations, however, results in asex winning under both stochastic and deterministic runs of the model for some combinations of parameters. The results reported in Table I show sex to be less protected under the stochastic model than for the deterministic model for a broad range of parameters. Finally, protection for sex increases with population size and declines under low mutation rates and less extreme forms of synergism.

The first set of runs examined the case of truncation selection for six combinations of mutation rate and population size. For $U=1.0$, sexual populations of sizes 10^3 and 10^4 were not protected under the deterministic model. Results from the stochastic model are similar in that sex was completely unprotected for population sizes of 10^3 and was protected only 1% of the time for population sizes of 10^4 . Under the deterministic model with $U=1.5$, sex was unprotected in populations of size 10^3 , but protected in populations of size 10^4 . In contrast to this, results from the stochastic model show that sex was protected 10% and 85% of the time in populations of size 10^3 and 10^4 , respectively. For $U=2.0$, sexual populations of

TABLE I
Fates of Invading Parthenogenetic Lineages under Three Different
Selection Regimes

U	N	\bar{n}	\bar{w}	i	% Sex	Deterministic
Truncation selection						
1.0	10^3	50	0.922	38	0	Asex
1.0	10^4	50	0.922	38	1	Asex
1.5	10^3	51	0.874	39	10	Asex
1.5	10^4	51	0.876	39	85	Sex
2.0	10^3	52	0.820	40	93	Sex
2.0	10^4	52	0.823	40	100	Sex
Intermediate selection						
1.5	10^3	39	0.548	26	5	Asex
1.5	10^4	39	0.545	26	8	Sex
2.0	10^3	41	0.461	28	57	Sex
2.0	10^4	41	0.467	28	98	Sex
Exponential-quadratic selection						
1.5	10^3	43	0.434	30	3	Asex
1.5	10^4	43	0.436	30	18	Sex
2.0	10^3	51	0.320	37	27	Sex
2.0	10^4	51	0.327	37	100	Sex

Note. All parthenogenetic lineages were initialized with a number of mutations corresponding to 2 standard deviations less than the mean for a freely recombining equilibrium sexual population. Variables included in this table are mutation rate per genome per generation (U), size of the sexual population (N), equilibrium mean number of mutations in sexual populations (\bar{n}), number of mutations in founders of asexual lineages (i), mean fitnesses of sexual populations (\bar{w}), percentage of time sex won in 100 runs of the stochastic simulation (% Sex), and the winner under the deterministic simulation (Deterministic).

size 10^3 and 10^4 were protected under the deterministic model. Under the stochastic model, sex was protected 93% of the time in populations of 10^3 , and was fully protected in population sizes of 10^4 .

The second set of runs examined the case of intermediate selection for four combinations of mutation rate and population size. Under the deterministic model with $U=1.5$, sex was unprotected in populations of size 10^3 , but not protected in populations of size 10^4 . Results from the stochastic runs, however, showed sex to be unprotected only 5 and 38% of the time for population sizes of 10^3 and 10^4 , respectively. For $U=2.0$ under the deterministic model, sex was protected in populations of size 10^3 and 10^4 .

In the stochastic runs, sex was protected 57 and 98% of the time for population sizes of 10^3 and 10^4 , respectively.

The third and final set of runs examined the case of exponential-quadratic selection for four combinations of mutation rate and population size. Results from the deterministic model for $U=1.5$ are identical to Charlesworth's (1990) result, and showed sex to be unprotected in population sizes of 10^3 and protected in population sizes of 10^4 . Results from stochastic runs, however, showed sex to be protected only 3 and 18% of the time for populations of size 10^3 and 10^4 , respectively. For $U=2.0$, sex was protected under the deterministic model for population sizes of 10^3 and 10^4 . Under the stochastic model, sex was protected 27 and 100% of the time for population sizes of 10^3 and 10^4 , respectively.

Finally, to examine the influence of stochastic processes on the rates at which newly established asexual lineages grow and accumulate mutations, I compared representative runs of the deterministic and stochastic models (Figs. 2 and 3). An inspection of Fig. 2 reveals that, for the stochastic runs, the initial population growth rate was higher in the successful asexual lineage than for the failed lineage, and that the initial population growth rate in the successful lineage is higher than would be predicted from the deterministic model. Similarly, Fig. 3 shows that the successful asexual lineage accumulated mutations less rapidly than the unsuccessful lineage, and that the rate of accumulation is lower than predicted by the deterministic model. While these runs were selected to highlight the effect that stochastic processes have on rates of initial population growth and the accumulation of mutations, the pattern is general.

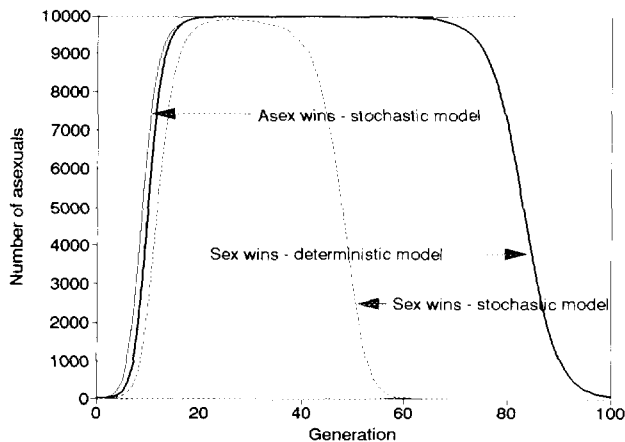


FIG. 2. Progress of asexual variants into sexual populations for representative runs of the deterministic and stochastic models. Mutation rates are 1.5 per genome per generation and population size is 10,000 for all cases. Selection is exponential-quadratic.

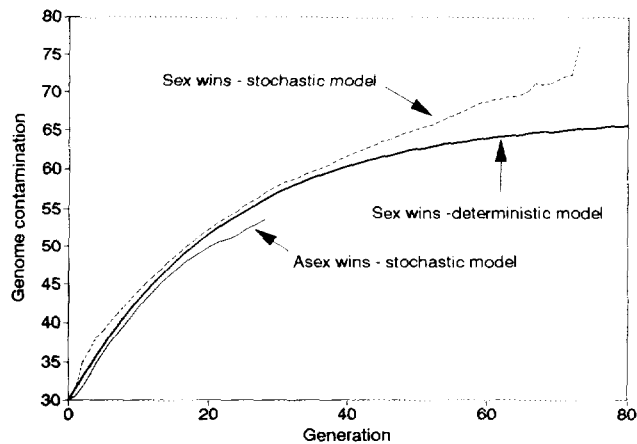


FIG. 3. Variation in rates at which mutations accumulated in asexual lineages for representative runs of the deterministic and stochastic models. Mutation rates are 1.5 per genome per generation and population size is 10,000 for all cases. Selection is exponential-quadratic.

Disagreement between deterministic and stochastic runs of the simulations appears to arise because of variation in one or both of these rates under the stochastic model.

DISCUSSION

Results from these simulations suggest that stochastic processes operating in finite populations can undermine protection for sex when mutation rates are less than about 2.0 per genome per generation. When asexual founders contain many mutations, or if mutation rates are sufficiently high, invading asexual lineages tend to arrive at mutation-selection balance and decline before displacing sexual populations. Lineages founded by individuals bearing few mutations, or those subjected to lower mutation rates, however, require more generations to achieve mutation-selection balance and can grow unimpeded for a period of time sufficient to displace the sexual populations from which they were derived. In cases where results from stochastic and deterministic runs are in disagreement, perturbations in the rates at which invading asexual lineages grow and accumulate mutations under the stochastic model appear to be decisive in determining the fates of invading asexual lineages (Figs. 2 and 3). Variation in these rates among replicate runs of the simulation can be attributed to random processes operating in small, newly established asexual lineages.

Ecological factors could interact with selection against deleterious mutations to protect sex when mutation rates are lower than about 2.0 or when asexual lineages are started with few mutations. One possibility is that competition is made less severe because asexuals suffer disproportionately from the effects of debilitating parasites. This may result from asexuals being inherently more susceptible due to hybridization and polyploidy, or from selection against common types as a result of coevolving parasites (Haldane, 1949; Clarke, 1976). Moritz *et al.* (1991) have shown that asexual populations of lizards are more susceptible to infection by mites than their sexual relatives, and Lively *et al.* (1990) reported that a trematode parasite differentially infected the most common phenotype in coexisting populations of sexual and asexual fish. Research from studies of crop plants provides evidence that monocultures suffer more from parasites (Barrett, 1981) and have lower yields than mixed stands of inbred lines (Wolfe and Barrett, 1980).

Another possibility is that sexual populations are able to persist in areas where parthenogens are absent or are inferior competitors. It is easy to imagine cases in which individuals either migrate into such areas or, in the case of small invertebrates and seeds of plants, are carried to them by animals or the wind. Case and Taper (1986) showed that asexual and sexual populations can coexist when depletion of resources by common genotypes leads to frequency-dependent fitnesses such that rare individuals gain an advantage. In either case, all that is required is that an asexual population be held at bay for sufficient time to allow its mutation load to increase to the point where it is susceptible to invasion by sexual competitors.

In conclusion, results from these simulations suggest that stochastic processes operating in finite populations have the potential to undermine protection for sex. To provide the sole explanation for sex, selection against harmful mutations may require mutation rates on the order of 2.0 per genome per generation. Sex may be protected under lower mutation rates, however, if one is willing to appeal to ecological factors as mechanisms for blunting the two-fold advantage of parthenogenesis until equilibrium conditions are achieved.

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